IL-17A Has Some Nerve!

James A. Sanford[1] and Richard L. Gallo[1,*]
[1]Department of Dermatology, University of California San Diego, La Jolla, CA 92093, USA
*Correspondence: rgallo@ucsd.edu
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Sensory neurons are important in controlling cutaneous inflammation, but the role of neurons in host antimicrobial defense was relatively unknown. Kaplan and colleagues now demonstrate that nociceptive fibers within the dermis play a crucial role in antifungal defenses through their influence on dermal dendritic cells and induction of IL-17A.

Mammalian skin is a densely innervated organ, but a clear and direct link between these sensory fibers and the cutaneous immune network has only recently been described. Notably, nerve fibers within the skin can play an essential role in maintaining inflammation since local denervation has been observed to result in a dramatic improvement in mouse models of psoriasis-like skin inflammation (Ostrowski et al., 2011). The mechanisms behind this observation were partially explained with the discovery that nociceptor sensory neurons induce IL-23 expression from dermal dendritic cells (dDCs). These dDCs in turn activate skin-resident γδ T cells to produce IL-17A, a major driver of psoriasiform inflammation (Riol-Blanco et al., 2014). These findings were further supported by clinical observations in humans that psoriatic plaques improve following local nerve damage. What remained unknown, however, was whether antimicrobial functions of the cutaneous innate immune response could be directly linked to the skin sensory nervous system.

An increasing body of evidence supports the conclusion that nerves can sense microbes. For example, it has been demonstrated that nerve fibers can directly sense bacteria via various membrane-bound receptors (Chiu et al., 2013; Meseguer et al., 2014). Activation of these fibers occurs before the onset of clinical inflammation, suggesting that sensory effects associated with bacterial infections are the result of direct microbial stimulation of neurons rather than a downstream effect of inflammatory processes. Indeed, in vitro and in vivo models have illustrated that bacteria and bacterial products result in rapid sensory responses including the induction of pain, vasodilation, and neuropeptide release (Chiu et al., 2013; Meseguer et al., 2014). Thus, it is becoming increasingly clear that the peripheral nervous system is capable of detecting the microbiome, and as a consequence it is in a position to influence innate immune processes present in the skin and other organs.

Kaplan and colleagues expand on this growing body of literature and demonstrate in this issue of *Immunity* that cutaneous sensory neurons can recognize *Candida albicans* and initiate IL-17-mediated protective immune responses (Figure 1) (Kashem et al., 2015). The authors show that neurons activate the CD301b$^+$ subset of dDCs to produce IL-23 that then drives IL-17A production from skin-resident γδ T cells. This study supports the concept that microbes are capable of directly stimulating neurons. Furthermore, the authors show that exposure to *Candida albicans* results in increased release of the neuropeptide CGRP, and that this is sufficient and necessary to induce IL-23 expression in dDCs. The study also identifies the specific DC subset (CD310b$^+$) that produces IL-23 and determines that γδ T cells, rather than Th17 cells or other cell types, are the predominant IL-17 producers. Deficiencies in any step of this pathway—neuronal activation and CGRP release, IL-23 production from dDCs, or IL-17A release from γδ T cells—results in a defective immune response and increased fungal burdens.

Th17 responses and the production of IL-17 family cytokines have a well-established role in cutaneous protection against numerous pathogenic microbes, including bacteria, fungi, and viruses. In particular, protection from chronic mucocutaneous candidiasis (CMC) seems to be strongly mediated by IL-17, as patients with a variety of conditions impairing Th17 cell development and function show increased susceptibility to infection with this microbe (McDonald, 2012). In addition to classical Th17 cells, innate sources of IL-17 production in the skin have been identified, notably various classes of γδ T cells including dendritic epidermal T cells (DETCs) (Gray et al., 2011; MacLeod et al., 2013). DETC-derived IL-17A plays an important role in the regulation of skin defenses and wound healing. This appears to be mediated in part through actions to induce antimicrobial peptide (AMP) production from epidermal keratinocytes (MacLeod et al., 2013). Although the present article from Kaplan and colleagues does not elucidate the mechanisms behind IL-17A-mediated killing of *C. albicans*, it is likely that AMP production and recruitment of phagocytic effectors to the site of infection are part of the processes involved in pathogen clearance.

Although the exact influences of sensory neurons on cutaneous immunity are still being elucidated, interesting information has arisen illustrating both beneficial and detrimental effects of their activation. On one hand, unwarranted inflammation driving the disease psoriasis appears to be worsened by neuropeptide release. This detrimental effect of neuron activation is illustrated by the observations that ablation of sensory neurons alleviates psoriatic inflammation (Ostrowski et al., 2011; Riol-Blanco et al., 2014). However, the problem with immune-dampening effects of neural ablation is illustrated in the data presented by Kaplan and colleagues as an attempt to treat disease by blocking nociceptive fibers predicts that this will leave the host more susceptible to infection with *C. albicans* (Kashem et al., 2015). Interestingly, activation of sensory neurons by *Staphylococcus*

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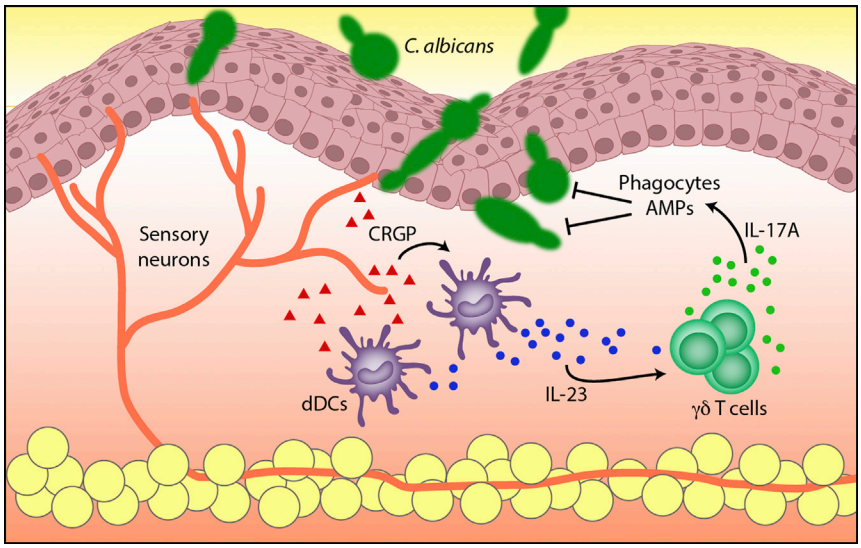

Figure 1. *Candida albicans* Stimulate IL-17A Production through Sensory Neuron Activation
Cutaneous nociceptor sensory neurons detect invading *Candida albicans*, resulting in the release of the neuropeptide calcitonin gene-related peptide (CGRP). CGRP stimulates CD301b$^+$ dermal dendritic cells (dDCs) to produce IL-23, which in turn activates skin-resident γδ T cells to secrete IL-17A, an important cytokine mediating antifungal defenses in the skin. AMPs, antimicrobial peptides.

aureus was demonstrated to exert immunosuppressive effects, as in this study neural ablation abrogated the pain response but led to increased cytokine production and inflammation (Chiu et al., 2013). This work did not investigate levels of γδ T cell-derived IL-17A, which has also been shown to be important in the innate immune response to *S. aureus* (Cho et al., 2010). It is interesting to consider that the context of the interaction between neural cells, immune cells, and microbes will be critical to predicting outcome. Certain pathogens might have evolved to utilize neural activation as a virulence factor or method to establish growth over other microbes. *S. aureus* pathogenesis might be enhanced by neural activation, whereas survival of *C. albicans* appears to be negatively impacted by these processes. In fact, co-infections with *S. aureus* and *C. albicans* are uncommon in immunocompetent patients.

It is well documented that psychological stress also has a negative impact on cutaneous immunity, as skin infections are more frequent and healing is delayed during prolonged periods of stress. Stress signals activate neuroendocrine circuits that result in decreased AMP production, leaving the skin more vulnerable to bacterial infections (Radek et al., 2010). Neuroendocrine circuits are distinct from the nociceptive fibers described in the current work. However, stimulation of different neural components of the skin might result in divergent effects on the immune system, thereby increasing or decreasing innate antimicrobial defenses.

An interesting question to be addressed in future work involves the underlying molecular aspects for *C. albicans* recognition by sensory neurons. Bacteria are detected by and activate these nerve fibers through a variety of mechanisms, including formyl peptide receptors (FPRs), LPS activation of Toll-like receptor 4 (TLR4) and the cation channel TRPA1, and direct perforation of cell membranes by pore-forming toxins. Meanwhile, it is known that immune cells sense *C. albicans* via TLR2 and dectin-1, but the expression of these receptors on sensory neurons has yet to be shown. It will be important to uncover the interactions between *C. albicans* and sensory neurons and determine whether different morphological forms or strains with varying virulence display altered ability to stimulate nociceptive fibers in the skin.

In conclusion, Kaplan and colleagues have contributed important new information to the growing body of evidence illustrating a complex neural-cutaneous immune axis, showing for the first time that a fungal pathogen activates sensory fibers to initiate an effective antimicrobial response (Kashem et al., 2015). These observations, and other data that have shown direct links between the nervous system and the immune system, demonstrate that in the skin the production of IL-17A has quite some nerve!

REFERENCES

Chiu, I.M., Heesters, B.A., Ghasemlou, N., Von Hehn, C.A., Zhao, F., Tran, J., Wainger, B., Strominger, A., Muralidharan, S., Horswill, A.R., et al. (2013). Nature *501*, 52–57.

Cho, J.S., Pietras, E.M., Garcia, N.C., Ramos, R.I., Farzam, D.M., Monroe, H.R., Magorien, J.E., Blauvelt, A., Kolls, J.K., Cheung, A.L., et al. (2010). J. Clin. Invest. *120*, 1762–1773.

Gray, E.E., Suzuki, K., and Cyster, J.G. (2011). J. Immunol. *186*, 6091–6095.

Kashem, S.W., Riedl, M.S., Yao, C., Honda, C.N., Vulchanova, L., and Kaplan, D.H. (2015). Immunity *43*, this issue, 515–526.

MacLeod, A.S., Hemmers, S., Garijo, O., Chabod, M., Mowen, K., Witherden, D.A., and Havran, W.L. (2013). J. Clin. Invest. *123*, 4364–4374.

McDonald, D.R. (2012). The Journal of Allergy and Clinical Immunology *129*, 1429–1435, quiz 1436–1427.

Meseguer, V., Alpizar, Y.A., Luis, E., Tajada, S., Denlinger, B., Fajardo, O., Manenschijn, J.A., Fernández-Peña, C., Talavera, A., Kichko, T., et al. (2014). Nat. Commun. *5*, 3125.

Ostrowski, S.M., Belkadi, A., Loyd, C.M., Diaconu, D., and Ward, N.L. (2011). J. Invest. Dermatol. *131*, 1530–1538.

Radek, K.A., Elias, P.M., Taupenot, L., Mahata, S.K., O'Connor, D.T., and Gallo, R.L. (2010). Cell Host Microbe *7*, 277–289.

Riol-Blanco, L., Ordovas-Montanes, J., Perro, M., Naval, E., Thiriot, A., Alvarez, D., Paust, S., Wood, J.N., and von Andrian, U.H. (2014). Nature *510*, 157–161.